

Serial No.: 09/293,670

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20. The method according to Claim 19, wherein said fluorescent protein is a green fluorescent protein (GFP).--

REMARKS

Claims 1-16 have been cancelled without prejudice, disclaimer or admission. New Claims 17-20 have been added, and consideration of these claims and the remarks that follow as they pertain to the new claims is respectfully requested.

Attached hereto is an appendix entitled "Version With Markings to Show Changes Made" which depicts the changes made to the present application by the current amendment.

Rejections under 35 U.S.C. §101

Claims 1-16 stand rejected under 35 U.S.C. §101 as not being supported by either a specific asserted utility or a well established utility. Applicants traverse.

The Office Action asserts that screening methods do not satisfy the utility requirements of 35 U.S.C. §101 until a bioactive agent having utility is identified by the use thereof. However, the Office Action provides no basis for such a requirement.

The Examiner's attention is respectfully drawn to the Utility Examination Guidelines, Federal Register, Vol.66, No.4, page 1098:

Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence regardless of publication date . . . to support the factual basis for the prima facie showing of no specific and substantial credible utility.

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. . . The prima facie showing must contain the following elements:

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- (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;
- (2) Support for factual findings relied upon in reaching this conclusion; and
- (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

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A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial and credible by a person of ordinary skill in the art in view of all the evidence of record.

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

As further stated in the MPEP at §2107.02, I, "the claimed invention is the focus of the utility requirement". Claims 1-16 have been cancelled without admission and the new claims are directed to methods for screening for an alteration in cellular phenotype, in accordance with the Examiner's recommendation in paper number 12, page 5.

The object of the claimed invention is screening for an alteration in cellular phenotype, wherein the phenotype is selected from the group consisting of cell cycle, apoptosis, exocytosis, expression of cell surface receptor, and reporter gene expression. Practice of the method steps effects the object of the invention by sorting cells by FACS and screening for an alteration in cellular phenotype. This screening is performed on the basis of at least five parameters. These parameters are described throughout the specification, e.g., page 10, line 34, to page 15, line 35; page 34, line 29, to page 42, line 23.

The methods involve the use of a population of cells comprising a library of retroviral vectors encoding candidate bioactive agents, where the detected alteration in the cellular phenotype is effected by a bioactive agent. While the new claims recite the use of candidate agents encoded by retroviral vectors, Applicants submit that other types of candidate agents may be

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used to effect alteration of the cellular phenotype which is to be screened for, and reserve the right to pursue claims along these lines in future prosecution.

Applicants point to *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), cited in the present Office Action, in which the court held that patentable utility requires that a process must be refined and developed to a point where specific benefit exists in currently available form. Applicants submit that the claimed methods for screening for alteration in cellular phenotype have utility in current form as being able to identify and separate cells altered in apoptosis, exocytosis, cell cycle, reporter gene expression, or cell surface receptor expression.

The specification provides an asserted utility for the methods, particularly elucidation of bioactive agents having activity for modulating or altering the cellular phenotype (for example see specification at page 8, lines 20-21).

The Office Action provides no evidence showing that this is an incredible utility or that the recited methods could not be used to elucidate bioactive agents having activity for modulating or altering the cellular phenotype. Further, the Office Action provides no evidence showing that the recited methods cannot be used for the object of the invention, namely screening for an alteration in cellular phenotype.

Moreover, with respect to the operability of the claimed invention, Applicants point out that the specification provides an example wherein a bioactive agent having well established utility as a modulator of cell cycle is identified by screening for an alteration in cellular phenotype. In the present example, cells are sorted by FACS and screened on the basis of five parameters for an alteration in cellular phenotype. Using this method, the alteration in cellular phenotype is identified and, further, p21 is identified as the bioactive agent capable of altering the cell cycle, thereby demonstrating the operability of the method. While Applicants hold that the asserted utility of the claimed screening methods satisfies the requirements of 35

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U.S.C. §101, the examples provided in the instant specification further support that the claimed invention has real world utility.

Finally, the Office Action states that the claimed invention lacks utility as the specification does not describe the structure, function or biological significance of bioactive agents provided by the screening methods and does not provide an intended use for such bioactive agents. In response Applicants point out that while the claims are not expressly directed to the identification of bioactive agents, as discussed above, agents that are identified by the use of the claimed methods for screening for alteration in phenotype have real world utility which is the ability to alter cellular phenotype. This is supported by the examples provided in the specification as discussed above.

Accordingly, Applicants submit that Claims 17-20 satisfy the utility requirements of 35 U.S.C. §101 and request withdrawal of the rejection and allowance of the claims.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-16 stand rejected under 35 U.S.C. §112, first paragraph. The Office Action alleges that the claimed invention lacks utility and that the artisan would accordingly not know how to make and use the invention. Applicants disagree with this allegation and respectfully traverse this rejection.

Claims 1-16 have been cancelled without prejudice, disclaimer or admission. For reasons set forth above, Applicants submit that the invention set forth by Claims 17-20 has practical utility. Applicants further submit that the artisan of reasonable skill in the art would be able to make and use the same and request withdrawal of the rejection and allowance of the claims.

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Rejections under 35 U.S.C. §112, first paragraph - written description

Claims 1-16 stand rejected under 35 U.S.C. §112, first paragraph as lacking written description support in the specification. Applicants disagree with this allegation and respectfully traverse this rejection.

Regarding Claims 1-16, the Office Action alleges that the claims are drawn to screening a population of altered cellular phenotypes altered by a candidate agent and are not supported by the specification, but admits that methods for the detection of alterations in cellular phenotypes are supported by the specification, for example at page 8, lines 12-18.

Without addressing the propriety of the rejection, in the interest of advancing prosecution, the new claims clearly recite “for an alteration”. Claims 1-16 have been cancelled without prejudice, disclaimer or admission and the new claims are directed to “methods for screening for an alteration in cellular phenotype in a cell”.

Claim 15 is rejected for use of the phrases, “different candidate agent” and “approximately simultaneously”.

Regarding the use of the “approximately simultaneously” phrase, Applicants submit that cancellation of Claims 1-16 obviates the rejection.

Regarding the recitation of “different candidate agents”, Applicants point out that the new claims recite the use of a library of retroviral vectors encoding different candidate agents. Applicants submit that the claims find support throughout the specification, for example, at page 19, line 8.

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Applicants submit that the new claims satisfy the written description requirements of 35 U.S.C. § 112, first paragraph, and request withdrawal of the rejection and allowance of the claims.

Rejections under 35 U.S.C. §112, first paragraph - enablement

Claims 1-16 stand rejected under 35 U.S.C. §112, first paragraph as lacking an enabling disclosure. The Office Action expresses that while being enabling for the use of p21 as bioactive agent with a specific tumor cell, the specification does not provide enablement for use of a library of candidate bioactive agents or nucleic acids and non-tumor cells.

Applicants traverse.

Claims 1-16 have been cancelled without prejudice, disclaimer or admission. The new claims are directed to the use of a population of cells comprising candidate bioactive agents encoded by retroviral vectors that provide for alteration in cellular phenotype. Cells are sorted by FACS, and screened on the basis of at least five parameters for alterations in cellular phenotype. Applicants reiterate that other types of candidate agents may be used to provide for alteration of cellular phenotype, and reserve the right to pursue claims along these lines in future prosecution.

The specification clearly describes what is meant by "candidate bioactive agent" or "exogenous compound", giving examples of types of candidate agents, describing categories of candidate agents, properties of candidate agents, sources of candidate agents, methods of obtaining or producing candidate agents, and modifications of candidate agents using a variety of fusion partners for a variety of purposes (see, e.g., the specification at page 16, line 10 to page 30, line 15).

Applicants submit that it would be clear to one of skill that the method steps of contacting the candidate bioactive agent to a cell (e.g., tumor cell or other), sorting a cell by FACS, and

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screening a cell on the basis of at least five parameters, does not require limiting the scope of the claims based on the description set forth in the specification, much less limiting the claimed method to the use of p21. Rather, the method steps provide for the use of a wide variety of candidate bioactive agents as set forth in the specification, which is an advantage of the invention.

Moreover, Applicants point out that a strength of the invention is that a library of candidate agents can be tested for an ability to alter cellular phenotype (as described in the specification for example, at page 31, line 30). Thus, a particular candidate agent need not be known to be effective with regard to altering cellular phenotype in order for the agent to be used in the claimed methods. The invention can be practiced with a mixture of known or unknown agents (for example a library comprising such a mixture) and can be used to elucidate bioactive agents that can alter cellular phenotype.

Accordingly, Applicants submit that enablement of the use of candidate agents other than p21 does not require teaching methods for first identifying agents that have phenotype altering activity.

Regarding the use of cell types other than tumor cell types in the screening methods, Applicants direct the Examiner to page 9, lines 14-17 and page 10, lines 10-13 of the specification. The specification clearly describes that a variety of cell types, including mixtures of cell types, are useful in the instant invention.

In addition, the Office Action provides no evidence showing that cell types other than tumor cell types could not be contacted with candidate bioactive agents in some way, or that cells so contacted could not be sorted by FACS, and screened on the basis of at least 5 parameters for an alteration in cellular phenotype.

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The Office Action provides no evidence showing that a library of retroviral vectors encoding candidate bioactive agents could not be used to provide for alteration in cellular phenotype, or that a population of cells comprising such a library of retroviral vectors could not be sorted by FACS and screened on the basis of at least 5 parameters for alterations in cellular phenotype.

Further, the Office Action offers no evidence to support that the use of agents other than p21 and cell types other than tumor cells would compromise the operability of the invention.

Applicants submit that the new claims are enabled in full scope by the instant specification and request withdrawal of the rejection and allowance of the claims.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-16 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Particularly, the Office Action alleges that it is not clear whether candidate bioactive agents or altered cells are being screened in the methods set forth by Claim 1 and dependent claims. Claim 1 is further rejected for allegedly not describing the basis by which a bioactive agent is considered a candidate, and for allegedly not clearly indicating whether altered or unaltered cells are referred to in step b. These same allegations form the basis for rejection of Claim 15 and dependent claims. Claim 2 is rejected for use of the phrase "a library of candidate bioactive agents" as allegedly being inconsistent with the phrase "candidate bioactive agents" that appears in Claim 1. Claim 4 is rejected for recitation of the library as a retroviral library as allegedly being inconsistent with Claim 3 reciting for "library of nucleic acids that encodes a candidate bioactive agent". Claim 16 is allegedly rejected for use of the phrase "approximately simultaneously". Applicants disagree with these allegations and respectfully traverse these rejections.



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Claims 1-16 have been cancelled without prejudice disclaimer or admission. The new claims recite "methods of screening for an alteration in cellular phenotype in a cell" in the preamble and recite method steps for sorting cells having an altered cellular phenotype. Applicants submit that the new claims clearly express that an alteration in cellular phenotype is being screened for, and request withdrawal of the rejection.

For the reasons discussed above, Applicants submit that methods for identifying agents as being candidate agents for use in the present methods are not required for enablement of the claims. Applicants further submit an expressed limitation on candidate agents need not be recited in the claims, for reasons set forth above. Applicants submit that the phrase "candidate agents" as recited in the claims and interpreted in view of the specification is definite and request withdrawal of the rejection.

Applicants submit that cancellation of Claims 1-16 obviates the remaining rejections and request withdrawal of the rejections and allowance of the new claims.

#### Double patenting rejections

Claims 1-3, 5 and 6 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-6, 12-23 and 35 of copending Application No. 09/062,330. Claims 1-7 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-3 and 5 of copending Application No. 09/157,748.

At such time as the subject matter of the provisionally rejected claims is allowed in the '330 or '748 applications, Applicants will terminally disclaim the corresponding claims of the present application.

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Provisional rejections under 35 U.S.C. § 103

Claims 1-7 stand provisionally rejected under 35 U.S.C. § 103(a) as being obvious in view of copending Application No. 09/157,748.

Applicants request that the rejection be held in abeyance as Applicants prepare to submit a declaration under § 132 to show that the relevant disclosure in the '748 patent is not the work of another.

Rejections under 35 U.S.C. § 102

Claims 1-4, 7-10, 13 and 14 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Nolan. Claims 3, 4, 10 and 14 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Kamb. Applicants disagree with this allegation and respectfully traverse this rejection.

In view of Nolan

The Office Action alleges that in Example 1, at page 51, Nolan discloses methods using FACS and supports that Nolan anticipates the instant invention.

The Office Action further alleges that at page 33, lines 19-28, Nolan discloses sorting cells by FACS using five parameters, namely:

- 1) survival protein;
- 2) expression of cell surface protein or other that can be rendered fluorescent or taggable for physical isolation;
- 3) death;
- 4) isolation of DNA; and
- 5) other cell viability dyes.

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Applicants disagree with the above allegations and assert that Nolan discloses sorting cells on the basis of a single parameter in Example 1 (i.e. content of fluoresceinated dUTP) and broadly describes methods for isolating a cell having an altered phenotype from the plurality of other cells (see, e.g., page 33, lines 19-28). FACS and expression of a survival protein are each merely listed as one of a number of methods for effecting isolation. The list of methods for effecting isolation has been erroneously interpreted, in the Office Action, as parameters for screening for an alteration in cellular phenotype.

In addition, the Office Action alleges that three parameters are inherent to prior art teachings using FACS, namely fluorescence, viability and apoptosis.

Applicants assert that the claims do not recite viability and apoptosis as parameters. Specifically, the claims recite phenotypes, including apoptosis. Further, viability is a state which may be determined by sorting cells by FACS on the basis of a described parameter, e.g., dye exclusion. Apoptosis is described as a cellular phenotype in the present invention, and alterations in apoptosis can be screened for by sorting cells by FACS on the basis of parameters including for example dye exclusion. Applicants submit that the prior art of record does not disclose the sorting of cells by FACS and screening on the basis of at least five parameters for the object of screening for an alteration in cellular phenotype.

In order for a reference to anticipate the claimed invention under 102(a), it must disclose each and every element within its four corners.

Applicants submit that Nolan does not disclose sorting cells by FACS and screening on the basis of at least five parameters for the object of screening for an alteration in cellular phenotype in a cell. Accordingly, Nolan does not recite the method steps of the instant claims and does not anticipate the instant invention. Applicants request withdrawal of the rejection and allowance of the claims.

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In view of Kamb

Claims 3, 8, 10 and 14, drawn to methods that involve sorting cells by FACS and screening on the basis of at least three parameters, stand rejected as being anticipated in view of Kamb. The Office Action alleges that Kamb discloses using four parameters to sort cells by FACS.

Without commenting on the propriety of the rejection, Applicants point out that Claims 1-16 have been cancelled without prejudice disclaimer or admission, and that the new claims are directed to methods involving sorting cells by FACS and screening on the basis of at least five parameters for an alteration in cellular phenotype.

Applicants submit that the current amendment obviates the rejection and request withdrawal of the rejection and allowance of the claims.

Rejections under 35 U.S.C. § 103

Claims 1-4, 7-10, 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Nolan. Claims 3, 4, 10 and 14 stand rejected under 35 U.S.C. § 103(e) as being obvious in view of Kamb. Claims 5-6, 11, 12, 15 and 16 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Kamb and Hide or Nolan and Hide. Applicants disagree with these allegations and respectfully traverse these rejections.

Standard for Obviousness

The criteria for establishing a *prima facie* case of obviousness are set forth in the MPEP at §2154:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable

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expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In view of Nolan

As discussed above, Applicants submit that Nolan does not disclose all elements of the claimed invention.

Nolan discloses a number of different examples of sorting cells by FACS on the basis of single parameter, for example the fluorescence a reporter such as GFP or fluorescein-labeled dUTP. Nolan does not explicitly suggest sorting cells by FACS and screening on the basis of at least four other parameters and does not explicitly disclose combining at least five parameters to provide a basis for screening for an alteration in cellular phenotype.

Accordingly, Applicants submit that Nolan does not disclose, individually or in combination, the elements of the claimed invention.

In addition, Applicants submit that no motivation is provided to add parameters in combination, to the fluorescence based FACS sorting taught by Nolan, to achieve screening for an alteration in cellular phenotype based on at least five parameters.

Notably, Nolan does not suggest sorting on the basis of combined parameters, for the purpose of measuring reporter expression in screening for an alteration in cellular phenotype.

Applicants submit that Nolan does not teach or disclose all elements of the claimed methods, and does not provide motivation to modify the teachings of Nolan to arrive at the instant claimed methods for screening for an alteration in cellular phenotype on the basis of at least five parameters. Applicants request withdrawal of the rejection and allowance of the claims.

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In view of Kamb

As discussed above with respect to the rejection under § 102(e) in view of Kamb, the current amendment cancels claims directed to methods involving sorting cells by FACS on the basis of at least three parameters. The new claims are directed to methods involving sorting cells by FACS and screening on the basis of at least five parameters for an alteration in cellular phenotype.

The Office Action alleges that Kamb discloses four parameters for sorting cells by FACS. Without addressing the propriety of the rejection, Applicants point out that Kamb does not suggest the at least five parameters of the instant claims, and as such does not teach all elements of the claimed invention. Accordingly, Applicants submit that the claimed invention is not obvious in view of the teachings of Kamb, and request withdrawal of the rejection and allowance of the claims.

In view of Nolan and Hide

Nolan is discussed above.

The Office Action alleges that Hide is added to Nolan "for the claimed limitation of the cellular phenotype as exocytosis and measuring said cellular parameter to detect forward and light scattering of cells to show the exocytosis effect of the cells."

Hide broadly teaches using flow cytometry to sort peritoneal mast cells based on measurement of 90 degrees light scatter. Without addressing the exocytosis disclosure of Hide, Applicants point out that Hide does not teach adding at least four parameters for screening for an alteration in cellular phenotype and, thus, cannot be combined with the teachings of Nolan to teach at least five parameters to provide a basis for screening as claimed

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in the instant application. As such, the combination of Nolan and Hide does not disclose all elements of the claimed invention.

Further, as discussed above with respect to Nolan, Hide does not suggest or motivate adding additional parameters in combination to fluorescence or 90 degrees light scatter, sorting cells by FACS, and screening cells on the basis of the combined parameters for an alteration in cellular phenotype.

The Office Action states that "one of ordinary skill in the art would have been motivated to measure another cellular parameters as light scattering by FACS when the cellular phenotype is caused by exocytosis to provide a clear or discernable effect of the cells."

Neither Hide nor Nolan teach or suggest that screening cells on the basis of additional combined parameters is useful for measuring degranulation or reporter expression, or for detecting an alteration in cellular phenotype.

Accordingly, Applicants submit that the combination of Nolan and Hide does not provide all elements of the claimed methods, and does not provide motivation to combine and modify the teachings of Nolan and Hide sufficient to arrive at the instant claimed methods for screening for an alteration in cellular phenotype based on at least five parameters. Applicants request withdrawal of the rejection and allowance of the claims.

In view of Kamb and Hide

Kamb and Hide are discussed above.

Applicants submit that the combination of Kamb and Hide does not provide all elements of the claimed methods, and does not provide motivation to combine and modify the teachings of Kamb and Hide sufficient to arrive at the instant claimed methods for screening for an

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alteration in cellular phenotype on the basis of at least five parameters. Applicants request withdrawal of the rejection and allowance of the claims.

### **CONCLUSION**

Applicants submit that the application is now in form for allowance and early notification of such is requested. If there remain issues that the Examiner believes may be resolved by telephone, he/she is respectfully requested to contact the undersigned at (415) 781-1989.

Respectfully submitted,

**FLEHR HOHBACH TEST**

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Dated: 11/17/02

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1. (cancelled) A method of screening a population of cells for at least one cell with an altered cellular phenotype, said method comprising:

- a) combining at least one candidate bioactive agent and a population of cells; and
- b) sorting said cells in a FACS machine by separating said cells on the basis of at least five cellular parameters which allow detection of alterations in cellular phenotype, whereby cells with altered cellular phenotype are identified.

2.(cancelled) A method according to claim 1 wherein a library of candidate bioactive agents are combined with said population.

3.(cancelled) A method of screening a population of cells for at least one cell with an altered cellular phenotype, said method comprising:

- a) introducing a library of nucleic acids each encoding a candidate bioactive agent into a population of cells; and
- b) sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters which allow detection of alterations in cellular phenotype, whereby cells with altered cellular phenotype are identified.

4.(cancelled) A method according to claim 3 wherein said library is a retroviral library.

5.(cancelled) A method according to claim 3 wherein said cellular phenotype is exocytosis and said cellular parameters are selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins.

6.(cancelled) A method according to claim 5 further comprising subjecting said cells to conditions that normally cause exocytosis.

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7.(cancelled) A method according to claim 3 wherein said cellular phenotype is cell cycle regulation and said cellular parameters comprise cell viability, proliferation, and cell phase.

8.(cancelled) A method according to claim 3, 4, 5, 6, 7, 11, 12 or 13 wherein said nucleic acids comprise fusion nucleic acids comprising:

- a) said nucleic acid encoding said candidate bioactive agents; and
- b) a detectable moiety.

9.(cancelled) A method according to claim 1 or 2 wherein said cells are tumor cells.

10.(cancelled) A method according to claim 8 wherein said detectable moiety is a fluorescent protein.

11.(cancelled) A method according to claim 4 wherein said cellular phenotype is exocytosis and said cellular parameters are selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins.

12.(cancelled) A method according to claim 11 further comprising subjecting said cells to conditions that normally cause exocytosis.

13.(cancelled) A method according to claim 4 wherein said cellular phenotype is cell cycle regulation and said cellular parameters comprise cell viability, proliferation, and cell phase.

14.(cancelled) A method according to claim 8 wherein said cells are tumor cells.

15.(cancelled) A method of screening for a bioactive agent capable of altering a cellular phenotype, said method comprising:

- a) combining at least one candidate bioactive agent and of a population of cells;

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- b) sorting said cells in a FACS machine by separating said cells on the basis of at least five cellular parameters which allow detection of alterations in cellular phenotype, whereby cells with altered cellular phenotype are identified and said alteration in cellular phenotype indicates said candidate is a bioactive agent capable of altering a cellular phenotype ; and
- c) optionally, repeating steps a) and b) with a different candidate bioactive agent.

16.(cancelled) The method of any one of Claims 1-7, 10-13 and 15, wherein measurement of each of said cellular parameters is done approximately simultaneously.

17. A method of screening for an alteration in cellular phenotype, said method comprising:

- a) providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents;
- b) sorting said population of cells based on at least five parameters; and
- c) detecting at least one cell of said population having said alteration in said cellular phenotype;

wherein said cellular phenotype is selected from a group of cellular phenotypes consisting of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene.

18. The method according to Claim 17, wherein said candidate agent comprises a fusion partner.

19. The method according to Claim 17, wherein said reporter gene encodes a fluorescent protein.

20. The method according to Claim 19, wherein said fluorescent protein is a green fluorescent protein (GFP).